In particular, claims 75 and 97 have been amended to more clearly reflect the invention as described in the specification. The phrase "disease or disorder" has been replaced by autoimmune disorder, proliferative disorder, or infectious disease. Support for the amendment is found at page 7, lines 11-12, page 16, lines 31-31, and section 5.9 at page 71, line 12 through page 72, line 2. The amendments and new claims are fully supported by the specification as originally filed, and, as such, no new matter has been added. In particular, support for the amendments is found at the following portions of the specification: page 80, lines 19-22; page 81, lines 32-35; page 82, lines 28-37; page 85, lines 32-36; and the data presented in Figure 9C. Support for new claim 129 is found at page 17, lines 12 and 13. Support for new claim 130 is found at page 19, lines 11 and 12. Support for new claim 131 is found at page 17, lines 14-17. Support for new claim 132 is found at page 11, lines 20-22.

Thus, claims 75, 97, 9-101, 104-112, 121, 122, and 129-132 are pending in the instant application. A marked-up version of the claim amendments is attached hereto as Exhibit A, showing deleted matter by brackets and added matter by underlying. A copy of the claims as pending is attached hereto as Exhibit B. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 75 and 97-128 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims. In particular, the Examiner contends that the specification, while being enabling for alpha 2 macroglobulin (α2M) and anti-CD91 antibody (α2M receptor antibody), does not reasonably provide enablement for any purified compound.

Applicants respectfully disagree and assert that, given the lists of compounds disclosed in the specification, i.e. small molecules, peptides, or antibodies (see page 7, lines 25-29 and section 5.2.3 page 40, line 14 through page 41, line 24) and the teachings found in the specification, one of skill in the art would be able to screen and identify compounds that could be used in the claimed treatment methods without undue experimentation.

However, without acquiescing to the propriety of the rejection of claims 75 and 97-128, and solely to advance prosecution and obtain coverage for certain specific embodiments

of the invention, Applicants have amended claims 75, 97, 104, 105, 107, 108, 110, 111, 121, and 122 to recite an anti-CD91 antibody, which antibody the Examiner has acknowledged is enabled. The amendments to the claims, combined with the cancellation of claims 98, 102-103, 113-120, and 123-128, renders the rejection moot. Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

Claims 97, 98, 102, 115, 117, and 126 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Examiner contends that the specification, while being enabling for gp96, HSP70, and HSP90, does not reasonably provide enablement for all heat shock proteins.

Applicants respectfully disagree with the Examiner's contention. The specification teaches heat shock proteins as a genus, defines the functional and structural characteristics of the genus, and provides working examples for several species, i.e. gp96, hsp70, and hsp90, within the genus (See page 1, lines 25 through page 2, line 15 of the application as filed). Thus, the specification is enabling for the genus that is heat shock proteins.

However, in the interest of advancing prosecution and obtaining coverage for certain embodiments of the invention, claims 98, 102, 115, 117, and 126 have been canceled, rendering the rejection moot with respect to those claims. In addition, claim 97 has been amended to recite an anti-CD91 antibody, and thus no longer recites compounds generally that modulate the interaction of an alpha (2) macroglobulin receptor and a heat shock protein. In light of the amendments, merely routine experimentation could be used to determine whether the antibody modulates such an interaction.

In summary, the claims, as amended, are fully enabled for the entire scope of the recited subject matter. Thus, for the reasons enumerated above, the rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claim 121 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner contends that the

specification does not provide any evidence of, or recite any specific utility, for any agonist that is capable of binding or modulating the interaction between α2M receptor and its ligand.

Applicants respectfully disagree. It would have been evident to the skilled artisan that the inventors had possession of the claimed method as amended, i.e., a method for treating or preventing an autoimmune disorder, proliferative disorder, or infectious disease comprising administering to a mammal an anti-CD91 antibody that binds alpha (2) macroglobulin receptor. Claim 121 has been amended to recite that the anti-CD91 antibody is an agonist. Anti-CD91 antibodies are taught in the specification (see page 28, lines 5-11).

In light of the amendment to claim 121, the foregoing remarks, the rejection under 35 U.S.C. § 112, first paragraph for lack of written description should be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 102, FOR ANTICIPATION SHOULD BE WITHDRAWN

Claims 75, 97, 104, 105, 107, 108, 110, 111, 113, 122, and 123 are rejected under 35 U.S.C. 102(b) as being anticipated by Pizzo (WO 94/14976; "Pizzo"). The Examiner contends that Pizzo discloses a method of treating or preventing infectious disease, autoimmune disease, or cancer, by administering a compound that binds to the alpha 2M receptor and modulates the activity of the alpha 2M recptor. Furthermore, the Examiner contends the Pizzo contemplates the use of antagonists because Pizzo discloses the use of antibodies capable of binding to the alpha 2M receptor. Applicants respectfully disagree.

Anticipation requires that all the elements and limitations of a claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). A prior genus which does not explicitly disclose a species does not anticipate a later claim to that species. See Donald S. Chisum, Chisum on Patents, § 3.02[2], at 3-21-22 (2002); *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988); *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1261, 9USPQ 2d 1962, 1970 (Fed. Cir. 1989).

Applicants submit that, contrary to the Examiner's contention, nowhere does Pizzo disclose the use of antibodies that bind to the alpha 2M receptor. Pizzo teaches enhancing the generation of antibodies to an antigen, by complexing the antigen to alpha (2) macroglobulin to form a complex. Pizzo further teaches that this complex, or antibodies to the antigen that are thereby generated, can be administered for purposes of treatment or prevention. The

antibodies taught for therapeutic use by Pizzo are not alpha (2) macroglobulin receptor-binding antibodies, but rather antibodies that recognize an epitope of an antigenic molecule that is complexed to alpha (2) macroglobulin. Pizzo neither discloses nor suggests an anti-alpha (2) macroglobulin receptor antibody or methods for using such an antibody to treat infectious disease, autoimmune disease, or proliferative disorder. Thus, claims 75, 97, 104, 105, 107, 108, 110, 111, and 122 as amended to recite methods which use an anti-CD91 antibody, are not anticipated by Pizzo.

In light of the forgoing remarks, the rejection under 35 U.S.C. 102(b) as being anticipated by Pizzo should be withdrawn.

4. THE REJECTION UNDER 35 U.S.C. § 103, FOR OBVIOUSNESS SHOULD BE WITHDRAWN

Claims 75, 97, 103-114, 116, 122, 123, and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pizzo (WO 94/14976) in view of Isaacs et al. (J. Biol Chem 1988 May;263(14):6709-6714; "Isaacs"). Applicants respectfully disagree, as discussed in detail below.

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

First, the relevant inquiry is: (1) whether the prior art suggests the invention; and (2) whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Second, the Federal Circuit has stated time and again that one cannot consider a reference in less than the entirety, *i.e.*, disregard disclosures in the reference that diverge from and teach away from the invention. Specifically, the Federal Circuit, stated, "It is impermissible within the framework of a Section 103 rejection to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other

parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art". *In re Wesslau*, 353 F.2d 238, 241 (CPCA 1965).

Third, the Federal Circuit has also held that the prior art must either expressly disclose every claim limitation or suggest modifications to meet every claim limitation. *Litton Indus. Products, Inc. v. Solid State Systems*, 755 F.2d 158, 164 (Fed. Cir. 1985). In *Litton*, the District Court found that a device was obvious by focusing on what "it thought was the 'most critical feature.'" The Federal Circuit reversed this decision because the cited references neither taught specific claim elements nor suggested to one of ordinary skill in the art the necessary modifications.

Finally, the Federal Circuit has also stated time and again that for the disclosures of two or more prior art references to be combined in order to establish *prima facie* obviousness "[t]here must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *In re Jones*, 21 USPQ2d 1941, 1943-1944 (Fed. Cir. 1992); *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) (Emphasis added). Moreover, the Federal Circuit has made very clear that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, at 1075.

Applicants respectfully disagree with the Examiner's rejection and submits that the instant invention is non-obvious over Pizzo in view of Isaacs. Applicants submit that, contrary to the Examiner's contention and as discussed above, nowhere does Pizzo teach the use of antibodies that bind to the alpha 2M receptor. Neither Pizzo or Isaacs provides a suggestion that an anti-CD91 antibody could be used *in vivo* to treat a mammal, much less used effectively or successfully to treat infectious disease, autoimmune disease, or a proliferative disorder. Moreover, one skilled in the art would not have had a reasonable expectation of success of achieving the claimed methods given the disclosure of Pizzo, which neither discloses or suggests an anti-CD91 antibody, or the disclosure of Isaacs, which discloses such an antibody only in the context of an *in vitro* assay designed to confirm the binding of the 7H11D6 antibody to a particular site on alpha (2) macroglobulin. While Isaacs tested the 7H11D6 antibody *in vivo*, no such experiments were conducted on the anti-CD91 antibody and no suggestion to conduct such experiments is provided. Isaacs does not disclose or suggest the use of an anti-CD91 antibody for treating infectious or preventing disease, autoimmune disease, or cancer. Moreover, neither Pizzo or Isaacs provides a suggestion to

combine methods disclosed in the references. Thus, it would not have been obvious to one of skill in the art at the time the application was filed, given the disclosure of Pizzo in view of Isaacs, that one could use an anti-CD91 antibody for treating or preventing disease.

In summary, Applicants submit that amended claims 75, 97, 104, 105, 107, 108, 110, 111, and 122 and new claims 129-132 recite an anti-CD91 antibody and are therefore not made obvious by Pizzo in view of Isaacs. Neither Pizzo or Isaacs suggest such antibodies for use in treating infectious disease, autoimmune disease, or a proliferative disorder. Pizzo and Isaacs do not expressly disclose every claim limitation or suggest modifications to meet every limitation of the amended claims. Furthermore, other claim limitations are not disclosed or suggested in either reference. For example, neither reference suggests antibodies that can modulate the interaction of an alpha 2M receptor and heat shock protein. Thus, the amendments to the claims in conjunction with the cancellation of claims 103, 113, 114, 116, 123, and 127, render the rejection under 35 U.S.C. 103(a) moot.

In view of the forgoing, the art relied on by the Examiner, does not render obvious the method of the claimed invention. Applicants therefore request withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

Applicants respectfully request that the present amendment and remarks be entered and made of record in the instant application. It is submitted that all the outstanding rejections have been obviated or overcome. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

It is believed that no fee is required for filing this Amendment. In the event a fee is required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: September 5, 2002

32,605
Adriane M. Antler (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures

EXHIBIT A
MARKED-UP VERSION OF THE AMENDED CLAIMS
U.S. Patent Application Serial No. 09/750,972
(Attorney Docket 8449-134)

75.(amended) A method for treating or preventing [a disease or disorder] an autoimmune disorder, proliferative disorder, or infectious disease comprising administering to a mammal [a purified compound, other than lactoferrin, tissue-type plasminogen activator, heat shock protein, a fusion protein comprising a heat shock protein, or a complex between a heat shock protein and a peptide, which compound] an anti-CD91 antibody that binds alpha (2) macroglobulin receptor, in an amount effective to treat or prevent the [disease or disorder] autoimmune disorder, proliferative disorder, or infectious disease in the mammal.

97. (amended) [A] The method of claim 75 [for treating or preventing a disease or disorder comprising administering to a mammal a purified compound, other than lactoferrin, tissue-type plasminogen activator, a heat shock protein, a fusion protein comprising a heat shock protein, or a complex between a heat shock protein and a peptide, which compound], wherein the antibody modulates the interaction of the alpha (2) macroglobulin receptor with a [first] heat shock protein[, in an amount effective to treat or prevent the disease or disorder].

99. (amended) The method of claim [98] 97, wherein the [first] heat shock protein is gp96.

100. (amended) The method of claim [98] 97, wherein the [first] heat shock protein is Hsp70.

101. (amended) The method of claim [98] 97, wherein the [first] heat shock protein is Hsp90.

104. (amended) [A] The method of claim 75, wherein the method is a method for treating or preventing cancer. [comprising administering to a mammal a purified compound, other than a heat shock protein, a fusion protein comprising a heat shock protein, or a complex of a heat shock protein and a peptide, which compound modulates the interaction of

alpha (2) macroglobulin receptor with an alpha (2) macroglobulin receptor ligand, in an amount effective to treat or prevent the disease or disorder in the mammal.]

105. (amended) [A] The method of claim 104, wherein [for treating or preventing cancer comprising administering to a mammal a purified compound, other than a heat shock protein, a fusion protein comprising a heat shock protein, or a complex of a heat shock protein and a peptide, which compound] the anti-CD91 antibody [binds] modulates the interaction of alpha (2) macroglobulin receptor with an alpha (2) macroglobulin receptor ligand. [, in an amount effective to treat or prevent the disease or disorder in the mammal.]

107. (amended) [A] The method of claim 75, wherein the method is a method for treating or preventing an infectious disease. [comprising administering to a mammal a purified compound, other than a heat shock protein, a fusion protein comprising a heat shock protein, or a complex of a heat shock protein and a peptide, which compound modulates the interaction of alpha (2) macroglobulin receptor with an alpha (2) macroglobulin receptor ligand, in an amount effective to treat or prevent the infectious disease in the mammal.]

108. (amended) [A] The method of claim 107, wherein [for treating or preventing an infectious disease comprising administering to a mammal a purified compound, other than a heat shock protein, a fusion protein comprising a heat shock protein, or a complex of a heat shock protein and a peptide, which compound] the anti-CD91 antibody [binds] modulates the interaction of alpha (2) macroglobulin receptor with an alpha (2) macroglobulin receptor ligand [, in an amount effective to treat or prevent the infectious disease in the mammal.]

110. (amended) [A] The method of claim 75, wherein the method is a method for treating or preventing an autoimmune disorder. [comprising administering to a mammal a purified compound, other than a heat shock protein, a fusion protein comprising a heat shock protein, or a complex of a heat shock protein and a peptide, which compound modulates the interaction of alpha (2) macroglobulin receptor with an alpha (2) macroglobulin receptor ligand, in an amount effective to treat or prevent the autoimmune disorder in the mammal.]

111. (amended) [A] The method of claim 110, wherein [for treating or preventing an autoimmune disorder comprising administering to a mammal a purified compound, other than

a heat shock protein, a fusion protein comprising a heat shock protein, or a complex of a heat shock protein and a peptide, which compound] the anti-CD91 antibody [binds] modulates the interaction of alpha (2) macroglobulin receptor with an alpha (2) macroglobulin receptor ligand. [, in an amount effective to treat or prevent the autoimmune disorder in the mammal.]

121. (amended) The method of claim 75, 97, 104, 105, 107, 108, 110 or 111 wherein the [purified compound] anti-CD91 antibody is an agonist of the alpha (2) macroglobulin receptor.

122. (amended) The method of claim 75, 97, 104, 105, 107, 108, 110 or 111 wherein the [purified compound] anti-CD91 antibody is an antagonist of the alpha (2) macroglobulin receptor.